

Invited Commentary

Chemotherapy Near the End of Life

First—and Third and Fourth (Line)—Do No Harm

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In reality, only 2 major reasons exist for administering chemotherapy to most patients with metastatic cancer: to help them live longer and/or to help them live better. In exchange



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for treatment-related toxic effects (as well as substantial time, expense, and inconvenience), chemotherapy can prolong survival for patients with a variety of—though not all—solid tumors. Chemotherapy may also improve quality of life (QOL) for patients by reducing symptoms caused by a malignancy. In this issue of *JAMA Oncology*, Prigerson and colleagues¹ report some troubling trial results: chemotherapy administered to patients with cancer near the end of life achieved neither goal.

The study team began with a group of 312 patients with progressive, previously treated, end-stage metastatic cancer and life expectancy of 6 or fewer months. Investigators followed them prospectively until death, assessing baseline Eastern Cooperative Oncology Group (ECOG) performance status, further chemotherapy use, and patient QOL in the week prior to death. Quality of life was assessed retrospectively by postmortem interview with the most knowledgeable caregiver. Adjusted survival time was not associated with chemotherapy use. Good (ECOG score = 1) baseline performance status was tied to lower QOL near death in patients who received chemotherapy (odds ratio, 0.35; 95% CI, 0.17-0.75), whereas chemotherapy was not associated with QOL in patients with poorer (ECOG score = 2-3) baseline performance status. The research team is to be commended for a well-conducted study involving a difficult but important issue.

Accepting the results of the study by Prigerson et al raises fundamental questions. Why did patients with end-stage cancer who received chemotherapy have the same observed survival as those who did not? It is important to note that this was a prospective cohort study not designed to definitively determine whether chemotherapy prolongs survival in patients with terminal metastatic cancers. The study included patients with a heterogeneous group of malignancies with differing chemosensitivities and divergent therapies. Chemotherapy itself was not defined in the manuscript, and targeted biologics were not specifically mentioned. We do not know why some patients received treatment and others did not, except that patients seen in academic centers were more likely to receive systemic therapy. At the same time, it is hard not to look at this study as the closest we are likely to come to obtaining proof of the real-world effectiveness of chemotherapy in patients at the end of life with cancer, as a placebo-controlled, double-blind, randomized trial seems unlikely. We believe the efficacy results by Prigerson et al are generally true, represent current prac-

tice, and stand as a relative indictment of routinely offering chemotherapy to patients with terminal cancers.

It is not surprising that chemotherapy did not improve QOL for most patients. The measurement focused on the last week of life, when one would presume that other biomedical, psychosocial, or spiritual issues were weighing heavily upon the patients. But why should patients with the best (ECOG score = 1) performance status have poorer QOL at the end of their lives when they received chemotherapy? One obvious possibility is that the patients were harmed by the treatment, but these data are insufficient to definitively attribute poorer QOL to toxic effects. Moreover, these data do not explain the differing results in the slightly healthier (ECOG score = 1) performance status group vs the less healthy group (ECOG score = 2-3). Did the former have further to fall? Regardless, it is obvious that receiving chemotherapy did not improve QOL for patients in aggregate.

We must ask why oncologists treat patients so late when life expectancies are very limited. In administering chemotherapy, we expect a trade-off. Patients might live longer at the cost of a brief decline in QOL from toxic effects. Patients might also feel better from a reduction of malignancy-related symptoms, even if they do not enjoy improved survival. But late-line therapy is not effective for many solid tumors, and the authors reference non-small-cell lung cancer (NSCLC) treatment as having a 0% to 2% response rate for third- and fourth-line use.² Similarly, data citing QOL improvement in patients with poor prognosis are limited. Regardless, it is disturbing that this trial demonstrated no benefits of chemotherapy for patients with solid tumors or poor prognosis, and it is disconcerting that oncologists still recommend and use systemic therapy so close to patient death.

What does this mean for clinical practice? Must we then just say no to late-line chemotherapy? In this trial by Prigerson and colleagues, subjects were eligible if they had a prognosis of 6 months or fewer, and about 60% of patients died during the unspecified observation period. However, oncologists cannot precisely predict life expectancies. One study showed that estimates of patient survival were inaccurate approximately 80% of the time.³ However, oncologists are better when asked to narrow time to 1 year or less.⁴ When oncologists were asked if they would be surprised if a patient with advanced cancer were to die within 1 year, a response of no identified patients who had a 7-fold greater risk of death in the following 12 months.⁴

Additionally, patients often want systemic treatment until the bitter end. We have long known a substantial minority of patients with incurable NSCLC would desire chemotherapy, even in the setting of severe toxic effects for a 1-week gain in survival.⁵ Similar data exist for patients with breast and

large bowel cancers. It is hard to say no to chemotherapy, because doing so could potentially make an oncologist feel they are depriving the patient of all hope. Importantly, this does not mean that the oncologist cannot have a meaningful conversation with most patients about prognosis, especially when there is suspicion that time is limited.

These data from Prigerson and associates suggest that equating treatment with hope is inappropriate. Even when oncologists communicate clearly about prognosis and are honest about the limitations of treatment, many patients feel immense pressure to continue treatment. Patients with end-stage cancer are encouraged by friends and family to keep fighting, but the battle analogy itself can portray the dying patient as a loser and should be discouraged.⁶ Costs aside, we feel the last 6 months of life are not best spent in

an oncology treatment unit or at home suffering the toxic effects of largely ineffectual therapies for the majority of patients. At this time, it would not be fitting to suggest guidelines must be changed to prohibit chemotherapy for all patients near death without irrefutable data defining who might actually benefit, but if an oncologist suspects the death of a patient in the next 6 months, the default should be no active treatment. Oncologists with a compelling reason to offer chemotherapy in that setting should only do so after documenting a conversation discussing prognosis, goals, fears, and acceptable trade-offs with the patient and family. Let us help patients with metastatic cancer make good decisions at this sad, but often inevitable, stage. Let us not contribute to the suffering that cancer, and often associated therapy, brings, particularly at the end.

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